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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|--------------|----------------------|---------------------|------------------|
| 10/723,365 | 11/26/2003 | Dirk van den Boom | SEQ-2073-UT | 4199 |
| 47328 | 7590 | 07/03/2007 | EXAMINER: | |
| GRANT ANDERSON LLP C/O PORTFOLIOIP PO BOX 52050 MINNEAPOLIS, MN 55402 | | | WOOLWINE, SAMUEL C | |
| ART UNIT | PAPER NUMBER | 1637 | | |
| MAIL DATE | | DELIVERY MODE | | |
| 07/03/2007 | | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

| | | |
|-----------------|-----------------------------|-----------------------------|
| Application No. | 10/723,365 | Applicant(s) BOOM ET AL. |
| Examiner | Art Unit Samuel Woolwine | 1637 |

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) The period for reply expires 5 months from the mailing date of the final rejection.
 b) The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. The Notice of Appeal was filed on 11 June 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) They raise the issue of new matter (see NOTE below);
 (c) They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. Applicant's reply has overcome the following rejection(s): _____.

6. Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. For purposes of appeal, the proposed amendment(s): a) will not be entered, or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 12-39 and 58-73.

Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
 See Continuation Sheet.

12. Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.

13. Other: See Continuation Sheet.

JEFFREY FREDMAN
PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's argument on page 12 of the response filed 6/11/2007 states: "the Zabeau reference does not provide any motivation to combine the Zabeau teachings with the use of compositional isomers". This argument is not persuasive, because it is not necessary that a motivation be found in the references themselves. Both the CAFC and the Supreme Court have recently reinforced that the "teaching, suggestion or motivation test" should not be rigidly applied. Rather, both courts emphasized the use of common sense in arriving at a conclusion as to obviousness.

In DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641 (Fed. Cir. 2006), the Court states at 1645: "In contrast to the characterization of some commentators, the suggestion test is not a rigid categorical rule. The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. In re Dembiczak, 175 F.3d 994, 999 [50 USPQ2d 1614] (Fed. Cir. 1999). As we explained in Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1472 [43 USPQ2d 1481] (Fed. Cir. 1997), 'there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art.'"

The Court further states, at 1650: "Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense."

And at 1651: "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

Likewise, the Supreme Court, in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), rejected the notion that a teaching, suggestion or motivation must be found in the prior art to render a combination of prior art teachings obvious. The Court states at 1395: "Neither the enactment of §103 nor the analysis in Graham disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half century, the Court has held that a "patent for a combination which only unites old elements with no change in their respective functions ... obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152 [87 USPQ 303] (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

Applicant's argument that Zabeau distinguishes the use of prior art methods that obtain these compositional isomers (also page 12 of the response) is not persuasive. Simply because Zabeau points out differences between his method and the use of compositional isomers does not mean that one would not have been motivated to incorporate compositional isomer analysis into Zabeau's method. Applicant emphasizes Zabeau's statement that the use of MS analysis to yield a "mass-fingerprint" "cannot be applied to diagnostic sequencing of nucleic acids, where the term diagnostic sequencing means the unequivocal determination of the presence, the nature and the position of sequence variations" (Zabeau page 4). Applicant asserts that, in contrast, the present invention does result in the determination of the presence, nature and position of sequence variations (top of page 13 of the response). However, this distinction between the present invention and Zabeau does not in fact exist. Applicant responded (page 11 of the response filed 09/08/2006) to an enablement rejection in an earlier Office action (OA 03/08/2006) in which the examiner argued that Applicant's invention was only enabled for cases in which some prior knowledge existed about the possible sequence variations likely to be found in a particular target sequence. Applicant at that time argued that, having performed Applicant's method, "a target nucleic acid may be found to have a sequence variation by first finding a fragment that is different from the corresponding reference fragment. Using methods of sequencing known in the art, and referenced in the background section of the specification, one of ordinary skill in the art would then be able to determine a sequence variation, even if there was no prior knowledge of such a sequence variation." Therefore, it appears that Applicant's method, as claimed and without any further steps of using "sequencing methods known in the art", would "at best" only reduce the number of possible compositional isomers". This is precisely what step g of currently amended claim 12 seems to do: determine a reduced set of possible compositional isomers (i.e. reduced set of sequence variations that are candidate sequences).

Applicant's remaining arguments on page 13 of the response filed 06/11/2007 point out that Zabeau cites references authored by Little, suggesting that because Zabeau points out differences between Little and his own method that one would not have been motivated to combine the two. However, as stated above, simply pointing out differences between the two methods does not teach away from the combination. The rejection pointed out a rational motivation as to why one would have been motivated to use Little's technique of correlating a particular sequence with a mass to determine sequence variation: this would obtain the benefit of deriving sequence information for diagnostic purposes (see OA 12/05/2006 at page 11).

Applicant's argument at the bottom of page 14 of the response that because Little does not teach cleavage into fragments as Zabeau, but instead teaches primer extension and is therefore non-analogous art, is not found persuasive. Both Zabeau and Little are concerned with using mass spectroscopy to gain sequence information for nucleic acids.

Applicant's disagreement with the examiner's interpretation of step g (top of page 14 of the response) is noted. However, the examiner

maintains the position that determination of a mass of a nucleic acid fragment inherently also determines a reduced set of sequence variations. For example, determining the mass of a nucleic acid fragment automatically excludes all possible nucleic acid sequences not having that mass. Applicant argues that this is not the same procedure as step g of currently amended claim 12. Rather, Applicant argues, Zabeau compares the mass spectra of one or more target nucleic acids with the mass spectra of the reference nucleic acid sequence by "systematic computational analysis" (page 7, lines 13-21 of Zabeau). However, it is unclear what other form "systematic computational analysis" could take other than to compare the obtained masses of the target sequence with the reference to derive the sequence of the target nucleic acid, which is the ultimate form of determining a reduced set of sequence variations that are candidate sequences?

Continuation of 13. Other: it is noted, as per the submission under 37 CFR 1.8(b)(3), that the reply filed 6/11/2007 was originally filed on 5/7/2007 with the United States Postal Service but was never received by the Office.